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Hydrogen bonding in 2-amino-4,6-dimethoxypyrimidine, 2-benzylamino-4,6-bis(benzyloxy)pyrimidine and 2-amino-4,6-bis(*N*-pyrrolidino)-pyrimidine: chains of fused rings and a centrosymmetric dimer

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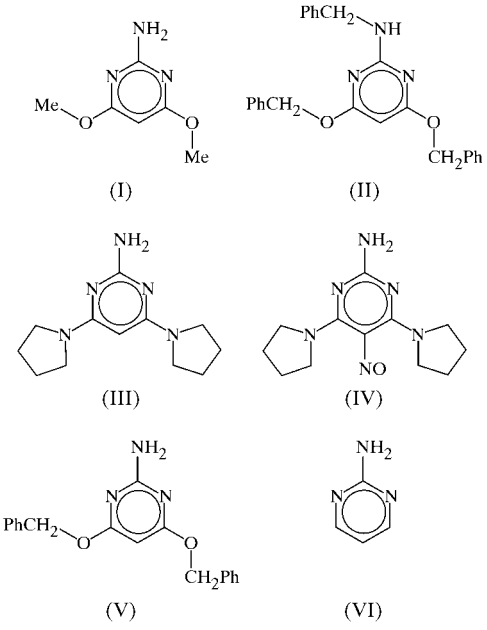
Molecules of 2-amino-4,6-dimethoxypyrimidine, $C_6H_9N_3O_2$, (I), are linked by two N—H···N hydrogen bonds [H···N 2.23 and 2.50 Å, N···N 3.106 (2) and 3.261 (2) Å, and N—H···N 171 and 145°] into a chain of fused rings, where alternate rings are generated by centres of inversion and twofold rotation axes. Adjacent chains are linked by aromatic π–π-stacking interactions to form a three-dimensional framework. In 2-benzylamino-4,6-bis(benzyloxy)pyrimidine, $C_{25}H_{23}N_3O_2$, (II), the molecules are linked into centrosymmetric $R_2^2(8)$ dimers by paired N—H···N hydrogen bonds [H···N 2.13 Å, N···N 2.997 (2) Å and N—H···N 170°]. Molecules of 2-amino-4,6-bis(*N*-pyrrolidino)pyrimidine, $C_{12}H_{19}N_5$, (III), are linked by two N—H···N hydrogen bonds [H···N 2.34 and 2.38 Å, N···N 3.186 (2) and 3.254 (2) Å, and N—H···N 163 and 170°] into a chain of fused rings similar to that in (I).

Comment

4,6-Dialkoxypyrimidines are key intermediates for the synthesis of a wide range of alkoxy and amino-substituted O^6-benzyloxy-5-nitrosopyrimidines (Marchal *et al.*, 1998, 2000; Quesada *et al.*, 2000), which are important as potential, or proven, *in vitro* inhibitors of the human DNA-repair protein O^6-alkylguanine-DNA-transferase (Chae *et al.*, 1995; Quesada *et al.*, 2002). Here, we report the molecular and supramolecular structures of two examples of this class of pyrimidine, namely 2-amino-4,6-dimethoxypyrimidine, (I), and 2-benzylamino-4,6-bis(benzyloxy)pyrimidine, (II).

Compound (I) could, in principle, adopt a conformation having C_{2v} (*mm*2) molecular symmetry. In the event, the conformations of the two independent methoxy substituents are such that there is no exact molecular symmetry, although there is approximate C_s (*m*) symmetry (Fig. 1 and Table 1). The C—N distances in (I) span the rather small range 1.331 (2)–1.355 (2) Å, with no significant bond fixation within the pyrimidine ring (Table 1). In this respect, the molecular–electronic structure of (I) is markedly different from those in a large number of analogous pyrimidines carrying a 5-nitroso substituent, where highly polarized structures are the norm (Low *et al.*, 2000; Low, Cannon *et al.*, 2001; Low, Moreno *et al.*, 2001; Quesada *et al.*, 2002).



The amino group in (I) acts as a double donor in N—H···N hydrogen bonds, while the two ring N atoms act as the acceptors. The O atoms play no part in the intermolecular aggregation (Table 2). Amino atom N2 at (x, y, z) acts as a hydrogen-bond donor, *via* atom H2*A*, to atom N1 at ($-x, 1-y, 1-z$), so generating a centrosymmetric $R_2^2(8)$ ring centred at ($0,\frac{1}{2},\frac{1}{2}$). This amino atom N2 at (x, y, z) also acts as a donor, this

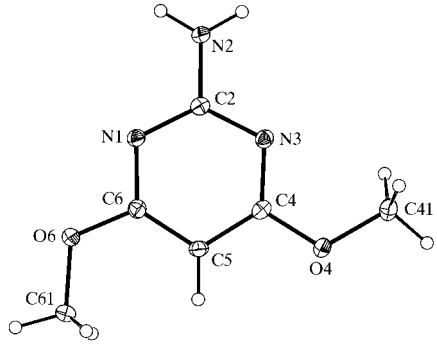


Figure 1
A view of the molecule of (I) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

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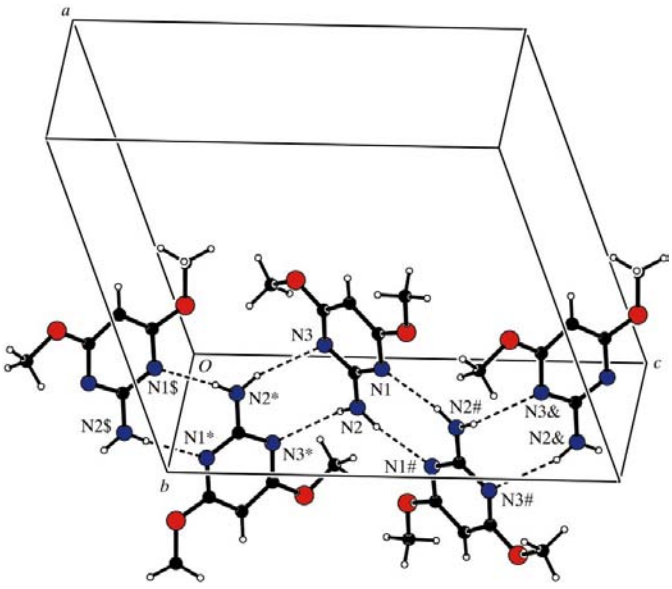

Figure 2
Part of the crystal structure of (I) showing the formation of a chain of fused rings along [001]. Atoms marked with an asterisk (*), hash (#), dollar sign ($) or ampersand (&) are at the symmetry positions $(-x, y, \frac{1}{2}-z)$, $(-x, 1-y, 1-z)$, $(x, 1-y, z-\frac{1}{2})$ and $(x, 1-y, \frac{1}{2}+z)$, respectively.

time *via* atom H2*B*, to atom N3 at $(-x, y, \frac{1}{2}-z)$, so producing a second $R_2^2(8)$ motif, generated by the twofold rotation axis along $(0,y,\frac{1}{4})$. Propagation of these two hydrogen-bonding motifs by inversion and rotation generates a chain of fused rings running parallel to the [001] direction (Fig. 2). The supramolecular structure can alternatively be viewed as a molecular ladder, in which paired $C_2^2(6)$ chains form the uprights and the C2—N2 covalent bonds form the rungs, so that the full graph-set designation is $C_2^2(6)[R_2^2(8)][R_2^2(8)]$.

Two chains of this type, related by the *C*-centring operation, run through each unit cell, along the lines $(0,\frac{1}{2},z)$ and $(\frac{1}{2},1,z)$, and the parallel chains are linked by aromatic π–π-stacking interactions to form a three-dimensional continuum. The pyrimidine rings of the molecules at (x, y, z) and $(\frac{1}{2}-x, \frac{1}{2}-y, 1-z)$ have parallel planes separated by 3.319 (2) Å; the centroid separation is 3.412 (2) Å and the centroid offset is only *ca* 0.79 Å (Fig. 3). In this manner, the chain along $(0,\frac{1}{2},z)$ is linked to each of the chains along $(\frac{1}{2},0,z)$, $(\frac{1}{2},1,z)$, $(-\frac{1}{2},0,z)$ and $(-\frac{1}{2},1,z)$, so forming a continuous bundle of chains.

In compound (II) (Fig. 4), atoms C27, C47 and C67 are also nearly coplanar with the pyrimidine ring, and the conformation of the alkoxy groups is similar to that in (I) (Fig. 4 and Table 3), although the phenyl groups each add two further rotational degrees of freedom. As in (I), there is no evidence of bond fixation or charge separation in the pyrimidine ring (Table 3). With only one N—H group per molecule available for N—H···N hydrogen-bond formation, the supramolecular structure of (II) is much simpler than that of (I). The molecules are linked by the hydrogen bonds into centrosymmetric dimers (Fig. 5 and Table 4), and there are no aromatic π–π-stacking interactions, so that the supramolecular aggregation consists simply of one finite zero-dimensional dimer per unit cell, with no direction-specific interactions between these units.

We also report here the structure of the closely related compound 2-amino-4,6-bis(*N*-pyrrolidino)pyrimidine, (III). We have recently investigated the structure of the 5-nitroso analogue, (IV) (Quesada *et al.*, 2002). However, not only were the crystals of (IV) obtainable only as a partial hydrate, of consistently poor quality [indeed, analogues of (IV) containing other secondary amino substituents cannot be crystallized at all], but the structure of (IV) was characterized by pseudosymmetry between the two independent molecules, by multiple disorder, both in the orientations of the two nitroso groups and in the conformations of the four inde-

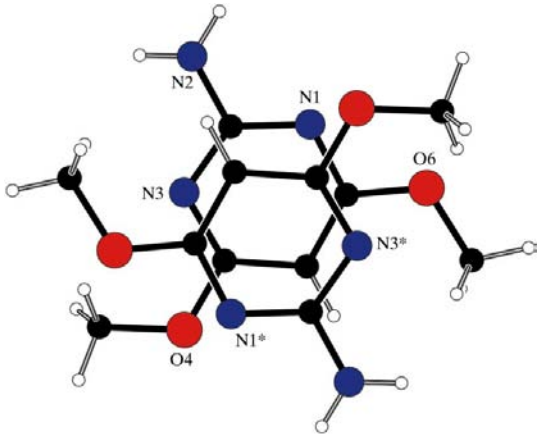

Figure 3
Part of the crystal structure of (I) showing the aromatic π–π-stacking interaction which links the [001] chains. Atoms marked with an asterisk (*) are at the symmetry position $(\frac{1}{2}-x, \frac{1}{2}-y, 1-z)$.

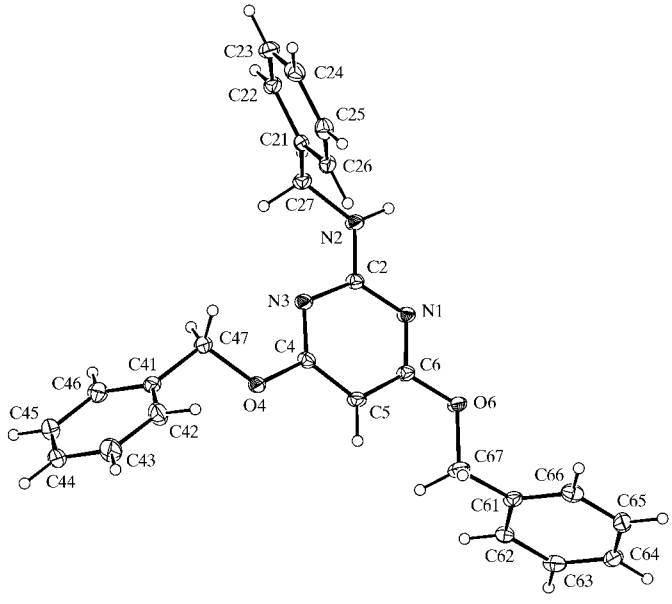

Figure 4
A view of the molecule of (II) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

pendent pyrrolidine rings, and by partial occupancy of each of the two independent water sites. Because of the poor diffraction data and the multiple disorder, no meaningful conclusions could be drawn about the intramolecular structural parameters for (IV), although the supramolecular structure, which takes the form of centrosymmetric six-molecule aggregates, was readily established.

In compound (III) (Fig. 6), by contrast, the intramolecular distances and angles are all well defined (Table 5). The four C—N distances within the pyrimidine ring, as well as the three exocyclic C—N distances involving three-connected carbon, all lie within the rather narrow range 1.346 (2)–1.359 (2) Å. This range of values is somewhat higher than the mean value of 1.333 Å for pyrimidines in general (Allen *et al.*, 1987) but, overall, the C—N and C—C distances within the pyrimidine ring of (III) are consistent with aromatic delocalization, with no significant bond fixation. At each of N4 and N6, the sum of the bond angles indicates planar N, consistent with the C4—N4 and C6—N6 distances (Allen *et al.*, 1987), and typical of amino N bonded to an aromatic or heteroaromatic ring. While the pyrrolidine rings exhibit the puckered conformation characteristic of saturated five-membered rings, there is no evidence, either from difference maps or from the displacement parameters, for any positional disorder of the C atoms in these rings. The CNC_2 planes centred on N4 and N6 are only very slightly twisted out of the plane of the pyrimidine ring (Table 5). The overall conformation of the molecule of (III) is very close to having local twofold rotational symmetry. This is illustrated not only by the torsion angles within the pyrrolidine rings (Table 5) but, perhaps more strikingly, by the location of the H atoms in these rings (Fig. 6). However, a search for possible additional symmetry revealed none.

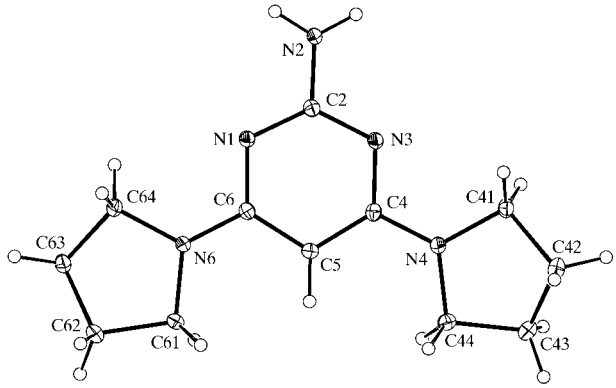

Figure 6
A view of the molecule of (III) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

The supramolecular structure of (III) takes the form of a chain of fused rings, similar to that found in (I). The amino group acts as a double donor in the intermolecular N—H···N hydrogen bonds, where the acceptors are the two ring N atoms (Table 6); the planar pyrrolidine N atoms play no part in the supramolecular aggregation. Amino atom N2 at (x, y, z) acts as a hydrogen-bond donor, *via* atom H2*A*, to ring atom N1 at (x, $1-y$, $-z$), so forming an $R_2^2(8)$ motif centred at $(0,\frac{1}{2},0)$. This amino atom N2 at (x, y, z) also acts as a donor, *via* atom H2*B*, to ring atom N3 at ($-x$, y, $\frac{1}{2}-z$), so forming a second $R_2^2(8)$ motif, this time generated by the twofold rotation axis along $(0,y,\frac{1}{4})$. The combination of these two distinct $R_2^2(8)$ motifs, one containing atoms N1 and N2 and the other containing atoms N2 and N3, generates a chain of fused rings

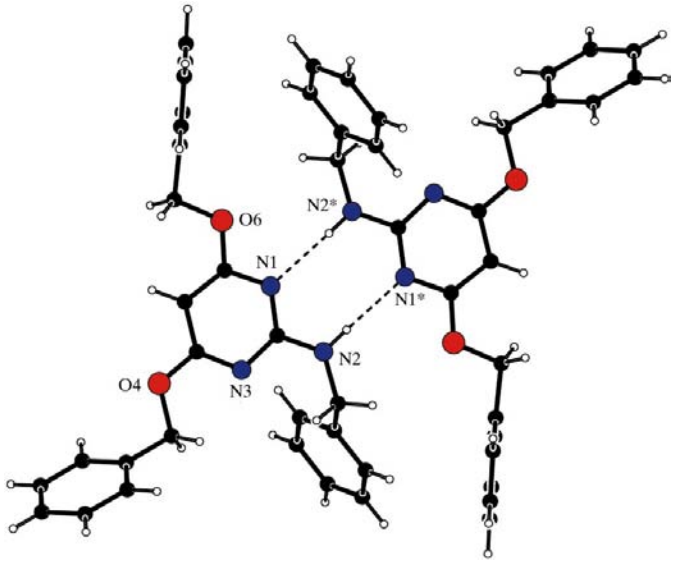

Figure 5
Part of the crystal structure of (II) showing the formation of a centrosymmetric dimer. Atoms marked with an asterisk (*) are at the symmetry position $(2-x, -y, 1-z)$.

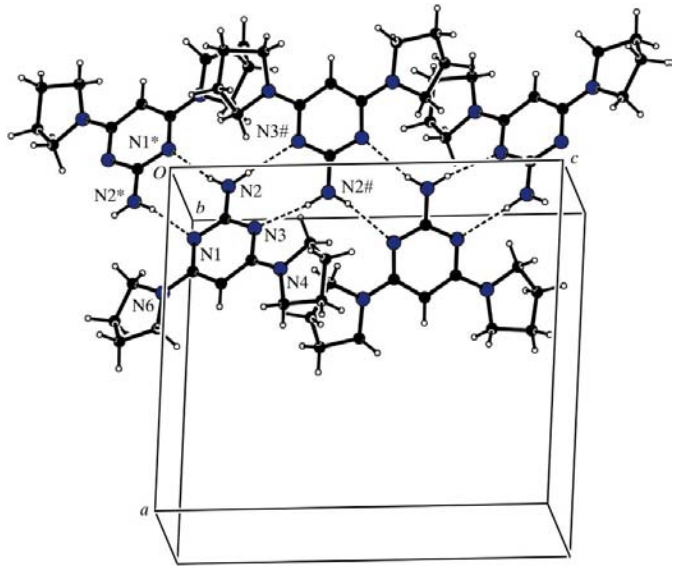

Figure 7
Part of the crystal structure of (III) showing the formation of a chain of fused rings along [001]. Atoms marked with an asterisk (*) or hash (#) are at the symmetry positions $(-x, 1-y, -z)$ and $(-x, y, \frac{1}{2}-z)$, respectively.

running parallel to the [001] direction (Fig. 7), generated by inversion centres at $(0,\frac{1}{2},\frac{n}{2})$ (for n = zero or integer) and twofold axes along $(0,y,\frac{1}{4}+\frac{n}{2})$ (n = zero or integer). Two of these chains run through each unit cell, but there are no direction-specific interactions between adjacent chains. In particular, the π–π-stacking interactions found in (I) are absent from the structure of (III). We note that this type of supramolecular aggregation would be possible even if the molecules of (III) had been located on twofold rotation axes.

It is of interest to compare the conformations and supramolecular aggregation in compounds (I) and (II) with those in the related compound (V) (Quesada *et al.*, 2002), which is analogous to (I) in containing an unsubstituted amino group, and to (II) in containing two benzyloxy substituents. In (V), where the conformation of the alkoxy substitutents is identical to those in (I) and (II), hydrogen-bonded $R_2^2(8)$ dimers precisely analogous to those in (II) are linked into a molecular ladder by N—H···O hydrogen bonds, with atom O4 as the acceptor. By contrast, the O atoms in (I) and (II) play no role in the hydrogen bonding, as noted above. Likewise, the supramolecular structures of (I), (III) and (V) can be contrasted with that of 2-aminopyrimidine, (VI), itself (Scheinbeim & Schempp, 1976; Furberg *et al.*, 1979). The molecules of (VI) act as double donors and double acceptors of N—H···N hydrogen bonds and two motifs are generated, by a centre of inversion and by a glide plane, leading to the formation of sheets.

Experimental

A sample of (I) was purchased from Aldrich. For the synthesis of (II), (I) (19.3 mmol) was added to a stirred solution of sodium benzylate (96 mmol) in toluene (100 ml). The resulting mixture was heated under reflux, with stirring, for 60 h. Diethyl ether (30 ml) and toluene (15 ml) were then added and the mixture was filtered through silica gel. The silica gel was washed with toluene (3 × 40 ml) and diethyl ether (3 × 40 ml), and the filtrate and washings were pooled together. After removal of the solvent, the oily residue was dissolved in a hexane–ethyl ether mixture (60:40 *v*/*v*) and cooled. The product, (II), precipitated at 253 K and was collected by filtration, washed with hexane and dried *in vacuo* (yield 70%, m.p. 355 K). Analysis, found: C 75.2, H 5.8, N 10.6%; $C_{25}H_{23}N_3O_2$ requires: C 75.5, H 5.8, N 10.6%. Spectroscopic analysis: ^{1}H NMR (DMSO-d_6, δ, p.p.m.): 4.46 (*d*, 2H, N—CH_2, J = 6.02 Hz), 5.27 (*s*, 4H, O—CH_2), 5.45 (*s*, 1H, C5—H), 7.29 (*m*, 15H, Ph), 7.75 (*t*, H, NH, J = 6.59 Hz, exchanges with D_2O); ^{13}C NMR (δ, p.p.m): 44.1, 66.7, 78.1, 126.4, 128,2, 136.8, 140.4, 161.2, 170.8. For the synthesis of (III), pyrrolidine (21.3 mmol) and triethylamine (18.3 mmol) were added to a stirred solution of 2-amino-4,6-dichloropyrimidine (Aldrich; 6.1 mmol) in *n*-butyl alcohol (40 ml). The resulting mixture was heated under reflux, with stirring, for 56 h. After filtration and removal of the solvent, hot ethyl acetate (100 ml) was added, and the product, (III), was filtered off (yield 68%, m.p. 497 K). Analysis, found: C 61.7, H 7.9, N 29.9%; $C_{12}H_{19}N_5$ requires: C 61.8, H 8.2, N 30.0%. Spectroscopic analysis: ^{1}H NMR (DMSO-d_6, δ, p.p.m.): 1.85 (*m*, 8H, CH_2), 3.27 (*m*, 8H, N—CH_2, partially obscured by solvent DMSO-d_6), 5.31 (*s*, 2H, NH_2, exchanges with D_2O); ^{13}C NMR (δ, p.p.m.): 24.6, 45.7, 73.2, 161.3, 161.6. Crystals of (I), (II) and (III) suitable for single-crystal X-ray diffraction were grown by slow evaporation of solutions in acetone, methanol and dichloromethane–ethyl acetate (1:1 *v*/*v*), respectively.

Compound (I)

Crystal data

$C_6H_9N_3O_2$
M_r = 155.16
Monoclinic, $C2/c$
a = 12.3971 (5) Å
b = 8.3608 (5) Å
c = 14.5237 (7) Å
β = 106.585 (3)°
V = 1442.75 (13) Å^3
Z = 8
D_x = 1.429 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 1642 reflections
θ = 2.9–27.4°
μ = 0.11 mm^{-1}
T = 120 (2) K
Block, colourless
0.20 × 0.15 × 0.05 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ scans, and ω scans with κ offsets
Absorption correction: multi-scan (*DENZO-SMN*; Otwinowski & Minor, 1997)
T_{min} = 0.978, T_{max} = 0.994
5248 measured reflections
1642 independent reflections
1090 reflections with $I > 2\sigma(I)$
R_{int} = 0.066
θ_{max} = 27.4°
$h = -16 \rightarrow 14$
$k = -9 \rightarrow 10$
$l = -17 \rightarrow 18$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.132
S = 1.01
1642 reflections
102 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0727P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.37 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (I).

N1—C2	1.338 (2)	C2—N2	1.342 (2)
C2—N3	1.355 (2)	C4—O4	1.342 (2)
N3—C4	1.331 (2)	O4—C41	1.437 (2)
C4—C5	1.386 (2)	C6—O6	1.3492 (19)
C5—C6	1.375 (2)	O6—C61	1.433 (2)
C6—N1	1.332 (2)		
C41—O4—C4—N3	−6.5 (2)	C61—O6—C6—C5	1.3 (2)

Table 2
Hydrogen-bonding geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2A···N1^{i}	0.88	2.23	3.106 (2)	171
N2—H2B···N3^{ii}	0.88	2.50	3.261 (2)	145

Symmetry codes: (i) $-x, 1-y, 1-z$; (ii) $-x, y, \frac{1}{2}-z$.

Compound (II)

Crystal data

$C_{25}H_{23}N_3O_2$
M_r = 397.46
Triclinic, $P\overline{1}$
a = 5.8083 (6) Å
b = 12.3104 (13) Å
c = 15.7260 (16) Å
α = 68.549 (2)°
β = 85.978 (2)°
γ = 82.737 (2)°
V = 1037.81 (19) Å^3
Z = 2
D_x = 1.272 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4785 reflections
θ = 1.8–29.0°
μ = 0.08 mm^{-1}
T = 120 (2) K
Needle, colourless
0.14 × 0.05 × 0.04 mm

Data collection

Bruker SMART 1000 diffractometer
φ scans, and ω scans with κ offsets
Absorption correction: multi-scan (*SADABS*; Bruker, 1997)
T_{min} = 0.989, T_{max} = 0.997
6639 measured reflections
4785 independent reflections
3697 reflections with $I > 2\sigma(I)$
R_{int} = 0.010
θ_{max} = 29°
$h = -7 \rightarrow 7$
$k = -13 \rightarrow 16$
$l = -20 \rightarrow 19$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.111
S = 1.07
4785 reflections
271 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0612P)^2 + 0.0805P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}

Table 3
Selected geometric parameters (Å, °) for (II).

N1—C2	1.3466 (15)	C2—N2	1.3424 (15)
C2—N3	1.3582 (15)	N2—C27	1.4495 (15)
N3—C4	1.3227 (15)	C4—O4	1.3516 (14)
C4—C5	1.3925 (17)	O4—C47	1.4522 (14)
C5—C6	1.3863 (16)	C6—O6	1.3530 (14)
C6—N1	1.3342 (15)	O6—C67	1.4470 (15)
C27—N2—C2—N3	−3.0 (2)	C67—O6—C6—C5	2.1 (2)
C47—O4—C4—N3	1.1 (2)		

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···N1^{i}	0.88	2.13	2.997 (2)	170

Symmetry code: (i) $2 - x, -y, 1 - z$.

Compound (III)

Crystal data

$C_{12}H_{19}N_5$
M_r = 233.32
Monoclinic, $C2/c$
a = 12.5654 (8) Å
b = 13.2735 (8) Å
c = 14.2279 (9) Å
β = 93.090 (2)°
V = 2369.6 (3) Å^3
Z = 8
D_x = 1.308 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2485 reflections
θ = 2.2–27.6°
μ = 0.08 mm^{-1}
T = 120 (2) K
Prism, colourless
0.3 × 0.2 × 0.2 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ scans, and ω scans with κ offsets
Absorption correction: multi-scan (*DENZO–SMN*; Otwinowski & Minor, 1997)
T_{min} = 0.975, T_{max} = 0.990
7257 measured reflections
2485 independent reflections
2109 reflections with $I > 2\sigma(I)$
R_{int} = 0.022
θ_{max} = 27°
$h = -16 \rightarrow 15$
$k = -16 \rightarrow 17$
$l = -15 \rightarrow 17$

Table 5
Selected geometric parameters (Å, °) for (III).

N1—C2	1.3464 (15)	C6—N1	1.3588 (14)
C2—N3	1.3506 (14)	C2—N2	1.3537 (15)
N3—C4	1.3484 (15)	C4—N4	1.3590 (14)
C4—C5	1.3965 (16)	C6—N6	1.3540 (15)
C5—C6	1.4035 (15)		
C4—N4—C41	123.39 (9)	C6—N6—C61	122.82 (9)
C4—N4—C44	123.91 (10)	C6—N6—C64	124.58 (9)
C41—N4—C44	112.62 (9)	C61—N6—C64	112.58 (9)
N3—C4—N4—C41	9.39 (16)	C5—C6—N6—C61	1.53 (17)
C5—C4—N4—C44	5.27 (17)	N1—C6—N6—C64	2.88 (16)
N4—C41—C42—C43	35.48 (12)	N6—C64—C63—C62	33.10 (11)
C41—C42—C43—C44	−40.59 (12)	C64—C63—C62—C61	−35.97 (12)
C42—C43—C44—N4	29.44 (12)	C63—C62—C61—N6	24.55 (12)
C43—C44—N4—C41	−7.37 (13)	C62—C61—N6—C64	−3.82 (13)
C44—N4—C41—C42	−17.80 (13)	C61—N6—C64—C63	−18.54 (12)

Table 6
Hydrogen-bonding geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2A···N1^{i}	0.88	2.38	3.2538 (14)	170
N2—H2B···N3^{ii}	0.88	2.33	3.1862 (13)	163

Symmetry codes: (i) $-x, 1 - y, -z$; (ii) $-x, y, \frac{1}{2} - z$.

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.117
S = 1.08
2485 reflections
154 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0753P)^2 + 0.6604P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}

Compounds (I) and (III) are monoclinic and the systematic absences permitted space groups $C2/c$ and Cc. For each, $C2/c$ was chosen and confirmed by the analysis. Compound (II) is triclinic; space group $P\overline{1}$ was selected and confirmed by the analysis. H atoms were treated as riding, with C—H distances in the range 0.95–0.98 Å and N—H distances of 0.88 Å.

For compounds (I) and (III), data collection: *KappaCCD Server Software* (Nonius, 1997); cell refinement: *DENZO–SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO–SMN*. For compound (II), data collection: *SMART* (Bruker, 1997); cell refinement: *SMART*; data reduction: *SHELXTL* (Bruker, 1997). For all compounds, program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2002); software used to prepare material for publication: *SHELXL*97 and *PRPKAPPA* (Ferguson, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1546). Services for accessing these data are described at the back of the journal.

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